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ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 4917

Title: A Case-Control Study of Factors that Trigger Flares of Inflammatory Bowel Disease

Reviewer code: 02495872

Science editor: Zhai, Huan-Huan

Date sent for review: 2013-08-01 21:46

Date reviewed: 2013-08-01 22:23

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

A well-written case-control study, focused on important problem.



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ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 4917

Title: A Case-Control Study of Factors that Trigger Flares of Inflammatory Bowel Disease

Reviewer code: 02440197

Science editor: Zhai, Huan-Huan

Date sent for review: 2013-08-01 21:46

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

The manuscript has studied the association between IBD flares and potential triggering factors. The results are of clinical significance.



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ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 4917

Title: A Case-Control Study of Factors that Trigger Flares of Inflammatory Bowel Disease

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Science editor: Zhai, Huan-Huan

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

Review of "A case-control study of factors that trigger flares...", Feagins et al This manuscript describes a clinic-based case-control study of IBD flares. Participants were IBD patients with or without ongoing flares; exposures potentially related to flares were assessed by recall during patient interview. The main finding is that the only significant trigger of flare is non-adherence to IBD meds. Major comments 1. The statistical treatment and presentation of results are unclear. Arguably the multivariable logistic regression results should be featured, not the crude (i.e., unadjusted) test of differences in proportions (Figure 1). It is fine to present results in a Figure instead of a table but please present the ORs for all exposures of interest from a single, mutually adjusted model. 2. The presentation of analysis methods (page 7) is unclear. It states that multivariate logistic regression was used, and variables were "evaluated." But does this mean they are in the same model and mutually adjusted, or does it mean a series of models each with just one independent variable were run? (The given reference for Bursac and colleagues is not helpful; if a variable selection procedure such as backward elimination was used, it should be described.) Was age or sex included? Why not consider IBD disease duration or race in the analysis of flares as well as in the adherence analysis? The selection of variables between these two analyses seems without justification. 3. Some potentially relevant factors are not discussed or are unclear in the analysis. Was logistic regression adjusted for age? What about BMI? Changes in diet? For NSAIDs use, were data gathered on dose, frequency of use, and etc or only "yes/no"? 4. In Results page 8, 1st paragraph it is noted that use of immunomodulators was higher in the control group. Is this to imply that use of other medications is a risk factor for flares (or conversely that immunomodulator use is more effective at preventing flares)? Wouldn't this be an important point? 5. Along the same lines, it is unclear how it can be



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concluded that non-adherence per se is the issue if one medication is better than the other and furthermore the class of medications is related to non-adherence. Ideally adherence would be compared between users of similar medications. But this is not clear in this study, and should be clearly detailed. 6. Discussion: page 10. "This prospective study..." is incorrect. The study described is retrospective because exposure information (e.g., adherence) was collected after incidence of disease (flares). Some of the data are perhaps prospective (from medical records) but on the whole it seems retrospective. Minor comments 7. P-values cannot be 1.0 (i.e., exactly 1). Please change to $P > 0.99$ or whatever the case may be. 8. Although the VA does provide access to treatment and medications it seems an overstatement to say variations in access "plays little role" in adherence. Isn't it possible that some veterans must travel far to reach the VA center in Dallas? If it takes a day off of work to drive 4 hours there and 4 hours back, for example, that is a big barrier. Would it be worth considering home address or distance traveled to the clinic? Or could more detail be provided on why the barriers within the VA system truly are low enough to be negligible? 9. Please include the number of patients invited to participate (Methods, page 6) and the response rate (or %).



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ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 4917

Title: A Case-Control Study of Factors that Trigger Flares of Inflammatory Bowel Disease

Reviewer code: 02529680

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Date sent for review: 2013-08-01 21:46

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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input checked="" type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input checked="" type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

This paper aims to explore the association between IBD inflammation flares and potential triggers. The research question is an important one given the physical, emotion, and economic costs of disease relapse. While the sample is relatively large and the question is of import, there are several major and minor ways the article could be strengthened. Below are questions, comments, and suggestions for the authors to consider.

ABSTRACT 1. The abstract is nicely written and sets up the paper well. Authors may want to reconsider the use of “definitively proven” in the abstract and introduction. This is the case with many studies of this nature and this study does not “definitively” prove triggers as well.

INTRODUCTION 2. The first paragraph is a little confusing and needs references. For instance, “Physicians may not systematically seek to identify triggers in their patients with IBD exacerbations, furthermore, and the causes of many exacerbations go unrecognized.” This seems like two different points that are related. Authors should consider breaking up points. Also, while this conclusion makes intuitive sense, is their empirical support for this statement? Authors should also reconsider the use of “importance” in the last sentence as the importance is clear.

3. Write out NSAIDs in Introduction. While it is written out in the abstract, acronyms should be written in text too.

4. A broader problem with the introduction is the lack of empirical review pertaining to all the triggers of an IBD flare. While type of medication and stress receive a large portion of the review, there is almost no information pertaining to why tobacco use and medication non-adherence contributes to a flare up. A more descriptive literature review of these possible triggers are necessary.

5. The aims and importance of this research could be strengthened. What is the impact of flares? Why should we care? The authors mention the veteran affairs health system offers a unique system in which to study patients, this transition seems awkward and it is not clear why this is the case. Also,



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what do the authors' mean by "patients who served in the military simply have to enroll and can receive free or low cost health care." Does this mean they have to enroll in the VA and receive medical treatment there? Or that they can enroll and receive free and low cost treatment. While I do not think the authors' mean study enrollment, it is confusing what enrollment refers to and the degree of choice. METHODS 7. On pg. 6, "The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) as reflected in a priori approval by the institutional review board of the Dallas VA Medical Center." all research has to adhere to these guidelines, not sure if this statement is necessary unless it is a journal guideline. 8. Recruitment requires more details. How and where were potential participants approached? How many individuals were approached? How many declined? 9. General study procedures are missing. Later in the manuscript an interview is mentioned. Who conducted the interview? It sounds like some information is self-report based on the interview, some information is collected from retrospective chart review, and disease activity is collected or generated? Did patients fill out any self-report measures? Did gastroenterologists complete disease activity forms at the time of the interview or is this done routinely? If disease activity was generated retrospectively, was any data checked by multiple raters to determine accuracy. Was written consent obtained? 10. Were labs collected as part of the study or where charts reviewed? If retrospective, what time frame was used to include a lab? What parameters were set for this? Stool assessment is unclear. Only 40 of flare group had this collected? This is not mentioned in methods. 11. Measures need citations, psychometric details, range of scores, et



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Name of Journal: World Journal of Gastroenterology

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Title: A Case-Control Study of Factors that Trigger Flares of Inflammatory Bowel Disease

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<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
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<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

The submitted manuscript tries to figure out trigger factors for an IBD flare in a cohort of patients evaluated at a veteran affairs institution. In this case control study encompassing 134 patients only medication non adherence was identified to be related to a disease flare, especially in ulcerative colitis. This finding is off relevance as it contradicts previous knowledge. Neither smoking nor NSAID use or stress factors had any impact which has been reported in the past. The paper is well written and offers no apparent criticism. Although the number of patients included is rather small it is no major drawback. However, the percentage of smokers is rather small. I assume, that the authors did not perform a matched analysis which would have improved the manuscript. Did the investigators observe a major recall bias? Hence, what was the ratio of invited/included patients in each group? Antibiotic use has been linked to the first diagnosis of IBD in general. Data regarding flares in established IBD is limited. The finding that immunomodulator use was more prevalent in the control group warrants some thoughts. In contrary, no difference was observed regarding biologics. This distribution should be mentioned in the discussion and highlights the efficacy of immunomodulators.